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Marked 'h' for human: Chimeric life and the politics of the human

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Abstract Chimeric life forms constitute mergers between two or more distinct beings. This article explores the making of interspecies mammalian chimeras in biomedical research where the availability of human embryonic stem cells and induced pluripotent stem cells has opened the way to radically humanize the biology of other organisms. By showing how chimeric life forms are foundational to biology, however, I loosen the compelling grip that chimeras have as liminal and monstrous. To the story of the chimera, this article replies with another story, that of the human as it is differently enacted at the levels of cells, tissues and organisms. Drawing on fieldwork conducted at a stem cell laboratory and farm animal research institute, the paper argues that meanings of the human become elusive and unknown when intertwined with chimeric life. In conclusion, the article reflects on the transforming politics of the human in biomedical research.
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Introduction

In order to dislodge us from our own species narcissism many working in critical and social theory have accepted the premise (to some degree or another) that the human can no longer serve as the basis and inspiration for social inquiry.[1] To understand the contemporary predicaments we find ourselves in we need to get away from the human. The life sciences have provided potent new sources of stimulation for such movements. However, as opposed to moving away from the human, translational biomedical research has ushered in a dazzling array of ways to model, create and organize research around the category human.

This article investigates recent transformations in how the human is defined, approached and governed in biomedical research by asking: what and who constitutes the human in the making of interspecies mammalian chimera? Within the fields of stem cell science and regenerative medicine, chimeric entities are made by inserting cells from one donor species

1 The dislocation of the human subject is not itself novel, having a long history in biological thought (e.g. Darwin, 1991) and other areas such as psychoanalysis (e.g. Freud, 1930). Perhaps more noteworthy about our contemporary moment then is the active and enthusiastic dislocation of the human subject seen across the humanities and social sciences via a variety of approaches: (Appadurai, 1988; Latour, 2007; Thrift, 2008; Bennett, 2009; Braidotti, 2013).

(such as human) into the developing embryo of another species (such as a pig). I explore how the generation of interspecies chimeras raises both scientific and political questions about the redefinition of human attributes, functions and processes at the molecular and cellular level.

In exploring the making of interspecies chimeric life, the article is organized around what historian and mythographer, Marina Warner (1994, p. 4) calls a cultural *kontakion*, a model of response and reply, invocation and challenge, based on the Greek antiphonal chorus sung across a church nave. This approach (replying to one story with another) is effective at the task of holding mythical nodes, such as the figure of the chimera, up to the light, in order to open up a new angle of view (Warner, 1994). The first section of the paper examines the mythic accretions gathered around the figure of the chimera and relates these to the experimental interspecies chimeras in mice, rats and birds that emerged in late twentieth century laboratories. These interspecies mixtures came to be known as chimeric (in direct reference to the Chimera monster of Greek myth) and have been central to establishing knowledge about the developmental and reproductive capacities of organisms. By showing how these chimeric forms of life are foundational figures in biology, I seek to loosen the compelling grip that chimeras have as liminal and monstrous.

To the story of the chimera, this article replies with another story, that of the human research subject as it is being re-specified across cellular and molecular levels. Chimeras, I will argue, are not so curious after all. They form a rather regular figure in biology since its inception. Instead, it is the category of human that has become elusive and unknown when entangled in chimeric life. Chimera-making technologies bring into question the relationship between the plasticity of biology and the human person. The case of interspecies mammalian chimeras presented here shows how these technologies both reify the category human but also confound previous biological and ethical settlements about how to approach and govern the human research subject in biomedicine. In concluding, the article reflects on recent scholarship that calls for explicit re-engagement with the category human in order to illuminate the politics of the human research subject in biomedical research.

The historical and ethnographic data on which this article is based comes out of a series of funded research projects carried out in Europe and North America which investigate recent transformations in how the human is defined and governed in biomedicine. The analysis presented here draws on a range of sources collected from these projects including: interviews with scientists, ethicists and lawyers, ethnographic and site observations, media articles, official reports and research guidelines. In northern Europe, ethnographic fieldwork took place in a publicly funded research consortium comprising a stem cell laboratory, a farm animal research institute and a primate research centre. In North America, laboratory visits with stem cell scientists, along with interviews with lawyers and ethicists, took place in major American research universities.[2] The historical review presented draws on bioscientific publications from the 1960s onwards that describe and report on interspecies

2 I conducted 35 interviews with stem cell scientists, veterinarians, animal husbandry experts, lawyers and research ethics committee members. Research visits between 3 weeks to 3 months were carried out in northern continental Europe and major US research universities. All the names of research participants that appear in the manuscript have been anonymised.

mammalian chimeras. In exploring the making of interspecies mammalian chimera, the aim of this article is not to uphold particular versions of what the human means, but rather to investigate what biomedical researchers take it to mean in their everyday practices.

She who lent her name to incongruous mixing

Who was Chimera? She was the daughter of Echida and Typhon. Echida, known in Greek mythology as the mother of monsters was half-woman and half-snake. She was the partner of Typhon, who was the last son of Gaia. Together Echida and Typhon brought many famous monsters into the world, including Chimera. Written about by Homer, Chimera, breathed fire from three heads and was "a thing of immortal make, not human, lion-fronted and snake behind, a goat in the middle" (Homer, Iliad 6.179–182). She lived on the hills of what is now south west Turkey in a series of caves. In Homer's tale, the hero Bellerophon kills the chimera by inserting a lump of lead into her throat where it cools, choking the monster to death. Chimera's fate, like many other monsters, was to meet death at the hands of a hero, but unlike her other monster kin, such as the Sphinx, Medusa and the Cyclops, Chimera ended up lending her name to a wide and generic concept – that of a heterogeneous being (Bompiani, 1989; Warner, 2007, p. 243).

In lending her name to the mixing of opposing parts and to unnatural assemblages, the term chimera has come to hold a strong purchase on social imaginations across many cultural epochs. In her study of monsters and myth, Warner (2007, p. 241–243) explains that since the Renaissance the word chimera has come to mean illusion itself – it is a monster that is "both frighteningly there and yet a spectre". Chimera is "the ultimate monster of monsters" (Warner, 1994, p. 10). From *Frankenstein's* monster, to the human-like creatures created by vivisection in the *Island of Dr. Moreau*, composite beings elicit both fascination and repulsion. However, they also do more than this. This is particularly true for Chimera. She was a remarkable monster because she is "the single character in a single story" who became "the protoype of every possible composite, every hybrid" (Bompiani, 1989, p. 377). The mythic accretions gathered around the term chimera have made their way deep into biology. For example, sex differences in biology are explained through the idea that females are cellular mosaics for X-chromosomal genes, leading to assertions that they are chimerical, mysterious and hence, duplicitous (Richardson, 2013, p. 110). As I will show below, the grip of the chimera on the modern imagination is evident across a range of different biological domains of thought.

Chimerism and horizontal life

While this article focuses on the technical composition of making interspecies mammalian chimeras, multiple forms of 'chimeric thinking' have increasingly become more widespread in the biological sciences. These are part of larger practical and epistemic changes in the life sciences themselves, what Nikolas Rose (2013, p. 19) calls an emerging style of thought characterized by "constant transactions across the apparent boundaries of the organism that constitute, shape and support vitality". Staffan Müller-Wille and Hans-Jörg Rheinberger

(2012, p. 206) argue that new approaches in biology have radicalized "the horizontalisation of hereditarian thinking and genetic practice" where "the entire gene pool brought about by evolution has become a universal tool box". In the contemporary life sciences, it is not just species boundaries that have become permeable, but also organic boundaries. Readily accepted since the nineteenth century, such assumed boundaries between microbes, plants and animals are now subject to renegotiation (e.g. Haraway, 1991; Ingold and Palsson, 2013; Landecker, 2015). Within this milieu, chimerism has emerged as a way to understand ourselves and other life forms (Hird, 2004; Landecker, 2007; Dupre, 2010; Margulis *et al*, 2011; Lappé and Landecker, 2015). While Müller-Wille and Rheinberger (2012, p. 206) insist that the future implications for molecular biology adumbrated in a term like chimeric "still lie beyond reckoning" such a term points to new developments in approaching and understanding hereditary materials in bioscientific research.

Drawing on forms of biological chimerism is an effective strategy for countering long-standing assumptions about the human body which have traditionally dominated in biomedical research. For example, in their discussion of symbiotic life, based on the work of evolutionary theorist, Lynn Margulis, Gilbert *et al*, (2012, p. 325) explain that we have never been biological individuals. Instead, humans, along with other organisms, are composites of many species (such as microorganisms) living and developing together – to this end, all organisms are chimeric and there are no monogenetic individuals (2012, p. 327). Philosopher of biology, John Dupré (2015, p. 70), also argues that the common understanding of an organism, truncated into the idea of one genome in one body is only one way to think about organisms. Dupre's argument is that we need to start thinking more about ourselves and the living things we share our environment with as polygenomic, or in other words, chimeric. Such arguments link to long-standing discussions in the philosophy of biology about what constitutes an individual (see: Pradeu, 2011). Dorian Sagan (1992, p. 364) has argued that the human body is 'chimerical': "Like that many-headed beast, the microbeast of the animal cell combines into one entity bacteria that were originally freely living, self-sufficient and metabolically distinct". Here the chimera is the eukaryote cell itself, but chimeric thinking, at the heart of symbiotic theories of life, is gaining traction in a variety of approaches that accentuate interconnected and interdependent forms of life. This can be seen in human/microbe relations with the recent popularity of Ed Yong's, *I contain multitudes* but also in biomedical research, where human health is coming to be defined through microbial partners (Benezra, 2016).

Chimeric life in biology represents genomic multitudes, defying conventional wisdom that there is only one genome in one organism (or body). This is significant because Anglo-American culture has taken the genome as a synonym for the self. Take for instance the BBC Futures special (Robson, 2015) on chimerism which opens with the line: "You may think your body and mind are your own. In fact, you are a fusion of many organisms - including, potentially, another person." This headline plays off the notion of merged twins in early development within the womb, where cells from two separate embryos collaborate to make only one individual. But does having the genetic material of a twin lost during early development mean you are two people? Writing on the history and politics of human chimeras in medical research, Aryn Martin (2007a, p. 205, 2007b) has pointed out just how curious such a leap is – why is it that journalists and even scientists "have come to equate genomes with selves and hence conclude that chimeras are more than one person"? Such a

leap she argues has to do with at least a half-century of gene-centric thought where we have come to think of ourselves as beings that possess a genome (unique to ourselves), and that we should protect this genome, sharing it only under certain conditions. Such thinking is typified by the title, J. Craig Venter, one of the first to sequence the human genome, gives his autobiography, *A Life Decoded: My Genome, My Life* (2007). However, a good decade and a half after the Human Genome Project's completion, the life sciences themselves stand in a moment of uncertainty, transition, and contestation – forcing a rethinking of the genome itself (Richardson and Stevens, 2015). In addition, there are a range of new biotechnologies, especially those providing the generation of different kinds of stem cells, which have opened new paths for the making of chimeras as both biological tools and for clinical application.

Experimental chimeras: technical research objects in cell and developmental biology

If we turn to the modern laboratories of the biosciences, chimeric entities are only one kind of mixture in a much bigger cast of characters. Chimeras exist within a broad spectrum of related biological entities, for example hybrids. A mule is a hybrid, as it is composed of homogenous cells that result from the fusion of an egg and a sperm of different species (a donkey and a horse) into a single zygote. Hybrids, however, are not regarded as chimeras because they do not contain genetically distinct cell populations. In chimeras, cells keep their distinct genetic identity. The sheep-goat chimera (or 'geep') is a good example of this. Created in 1984, this animal chimera had cells from both goat and sheep and thus could be used to test the effect of chemicals on both animals (Fehilly *et al*, 1984).

The systematic study of chimeric mammals began in the 1960s with mice. The mouse, wrote Andrzej K. Tarkowski (1998, p. 904) is "the unquestionable leader and hero among experimental mammalian chimeras". Tarkowski oversaw the first birth of these hero mice in 1961 in the Department of Zoology at what is now Bangor University in Wales:

> At that time, the idea of making one mammalian individual by aggregating two cleaving embryos must have looked rather preposterous and later I often wondered why Professor Rogen F. Brambell, under whose supervision I worked had accepted this and other crazy projects which I proposed to carry out in his laboratory (1998: 903).

These early chimeras were made by removing the thick transparent membrane surrounding two mammalian ovum and pushing the sticky embryos together, which then merged to form a single chimeric embryo. Tarkowski combined embryos from albino mice and embryos from another coloured strain, and examination of the retinas of these mice yielded morphological evidence of chimerism.

The term chimaera was used by Tarkowski in his 1961 paper, in contrast to Beatrice Mintz, another scientist, who separately, but at the same time as Tarkowski, created mice derived from embryo aggregation (Tarkowski, 1961; Mintz, 1967). Reflecting on the creation of these experimental mammals some 37 years after their initial birth, Tarkowski (1998, p. 904) suggests that such creatures were: "in a way a bow and a tribute paid by experimental embryology to ancient mythology which created monsters of dual, triple or even multiple origin". He defends the adoption of the "mythological term" chimera by

embryologists, pointing any doubters to the work of bird embryologists who can "produce chimeras closely resembling the mythological creatures, for instance an embryo with a chick head and neck on a quail body" (1998, p. 905).

It was during the 1970s that biologists developed chimeras to study cell lineage and cell fate during embryonic development. The late Anne McLaren began her 1976 book *Mammalian Chimaeras* by noting how biology, as well as mythology, provides examples of "the strange and often intimate associations between different species" (1). Her introduction notes that only a few dozen people in the world, who have worked with experimental mice chimeras, will share her enthusiasm for:

> their beauty, their unexpectedness, the insight they provide into old questions, and above all new questions, questions that one never dreamt existed in the days when an individual had two parents only (1976: 2).

For McLaren, experimental mice chimeras could be used to explore ideas about generation, reproduction and evolution because they were composite animals in which different cell populations are derived from one or more fertilized eggs. For experimental embryology, chimeras provided a method to understand and trace two cell populations in the fate of tissues and cell linage in development. For developmental genetics, chimeras provided another method to see how genetically different cells collaborate to form an adult animal. In 1976, McLaren was the sole author of *Mammalian Chimaeras*, but in 1984 she published another book on *Chimeras in Developmental Biology* with the biologist, Nicole Le Douarin, who developed chicken and quail chimeras (Douarin and McLaren, 1984). This collection had 21 authors, signifying the fast and multidirectional development of experimental chimeras in both mammals and birds.

Along with experimental embryology and developmental biology, transplantation biology relied heavily on chimeric entities. In the twentieth century, the mouse body became the host for many materials, especially in studies of immunological tolerance.[3] Using mice to foster human cells in a wide variety of contexts underwent a further revolution with the development of severe combined immunodeficiency (SCID) mice as a model organism (McCune *et al*, 1988). These mice are born with no immune system and are routinely used in cell transplantation research and studying the effects of disease on mammalian systems. SCID mice are a naturally occurring strain of mouse, a mouse mutant that has no human genes added.[4] The SCID mouse, with its capacity for humanisation is a living, integrated systems for transplantation biology, along with testing chemical compounds (Davies, 2012). Such living, integrated systems have now moved far beyond mice, with the development of neural, embryonic and germline chimeras that integrate human cells and tissues in a wide range of other animals (e.g. Povlsen *et al*, 1974; Ourednik *et al*, 2001; Nagano *et al*, 2002).

Chimeras continue to be used as a tool for biological knowledge. For example, one standard method for testing whether human embryonic stem cells are pluripotent is to inject them into immune-deficient mice, and see whether they give rise to a tumour that has all three embryonic germ layers. Researchers at Harvard's Stem Cell Institute were thus slightly

3 Peter Medawar transformed the practice of modern medicine through experiments on the immunological response of successful skin transplantation between different strains of mice and how 'foreign' antigens could be perceived as 'self' (Billingham *et al*, 1953). This work is also discussed in Landecker, 2007.

4 Humans also suffer from severe combined immunodeficiency where it is colloquially known as 'bubble boy' disease.

perplexed when a newly formed ethics committee, charged with overseeing human stem cell research, asked them to provide justification that this test did not endow 'human like' capacities in the mice they were using for this test of pluripotency. The group published a response to this question in the journal *Cell Stem Cell*, arguing that while technically doing such a test does create a 'human-animal chimera', it is not one that has human-like capacities and as such should be under the jurisdiction of animal care and use committees and exempt from formal review by the stem cell research oversight process that has recently begun to take root in the USA (Lensch *et al*, 2007).

While the chimera has a long history as a fantastical entity, the twentieth century history of biology shows how it has supported the making of the factual. In this way, the chimera has a double role in biology. It continues to represent, what Warner (2007, p. 243) calls the "fascination with the fantastic", but it has also provided the grounds to establish the facts and basis of reproduction and embryonic development. In this way, chimeras have played a fundamental role in shaping how we come to think about ourselves, and other organisms. In the spirit of Warner's method then, if the chimera is the technical and conceptual response to the demands of contemporary biomedical research, what kind of reply is invited by the figure of the human, to which Foucault (1970) argued, was the unspoken premise of much modern knowledge?

Making mammalian interspecies chimeras

Researchers working on the making of mammalian interspecies chimera are at the forefront of new approaches that combine fundamental biology and clinical application for human health. These are made by taking donor stem cells (for example, human donor cells) and implanting them into a pre-natal host embryo from another animal. While researchers have been looking at ways to produce human tissues for transplant for a long time, the recent successful growth of a rat pancreas in a mouse galvanized those working on interspecies chimera. In 2010, a research team reported on how they injected reprogrammed rat stem cells into mouse embryos where the gene for regulating pancreatic development had been deleted (Kobayashi *et al*, 2010). Some of the mice born survived into adulthood with functional pancreases that were almost completely composed of rat cells.

When I visited a consortium of European researchers working in regenerative medicine this paper, along with a similar one using pigs (Matsunari *et al*, 2013) was mentioned numerous times to me in discussions as a proof of concept for potentially cultivating human organs in other animals. The research consortium was comprised of stem cell laboratories and a farm animal institute for genetic research. Similar to others working in this field, these researchers sought to mix human stem cells into very early pig embryos and let them develop with idea of creating a 'bespoke pig' with a human organ that is genetically identical to an existing intended human recipient. By adding human donor cells into a developing embryo of a pig, which had been edited to have certain developmental pathways 'knocked out', the human cells would essentially fill in the gap (like the mouse with the rat pancreas). The creation of a pig with a human organ that is genetically identical and immunologically compatible with an existing intended human recipient would solve the problem of organ scarcity. There would also be no need for patients to have immunosuppressive treatment.

After all, the organ would already be their own. Such a chimeric animal (named as such because it would be a single organism composed of genetically distinct cells) has not yet been fully realized, but a range of foundational forms of research and proof of concept work are underway bringing human and non-human biological materials together across molecular, cellular and organismal levels.

At the stem cell lab some of this work involves the cultivation of human heart cells. During one of my laboratory visits, Sophie, who leads a project on bioanalytical techniques for tissue engineering and stem cell technologies, invited me to see these cells. Once in her lab, amid the din of extractor fans, she opened an incubator, pulled out a dish marked with 'h' for human and placed it under a microscope. Leaning in for a look, I saw small groupings of cells pulsating. Surprised at this movement, I pulled back. Sophie smiled and explained that these pulsating cells are cardiomyocytes. They form the muscle cells of our hearts and by pulsating the cells pump blood through our bodies, keeping us alive. These beating clumps were special because they were not always human heart cells. While they were always of human origin, (a human donor gave the original material) they were originally blood cells. These donor cells were then induced into a pluripotent state, a state where given the right kind of conditions, cells can be transformed into almost any kind of cell in our bodies.[5]

Once the human cells are cultivated, other lab members inject these materials into mice in order to test out ideas for cardiac tissue repair. Unlike some other vertebrates, who can generate their hearts after injury, the adult human heart has little capacity for regeneration. Putting human cells into the hearts of mice, however, takes a great amount of surgical skill. Mice hearts are small and beat fast. From their experiments, the researchers have concluded that the engineered human heart cells cannot really cope on a mouse heart. The mouse heart beats at 500 times a minute and a human heart at 60. Because of this, the tiny mouse heart expels the human cells from the target areas. The injection of human cells into mice results in a chimera – an organism that contains cells, which have different DNA from two separate origins. Now these particular animals' lives are short-lived, they are but momentary chimeras. After one to 2 weeks, the researchers sacrifice the mice to look at where and how the implanted cells are functioning.

Returning the pulsating cells to the incubator, Sophie pulled out another dish. This dish had a small platform with two titanium pegs on each end. Between the pegs, no bigger than my pinky nail was something pink. While I'm looking through the microscope, Sophie explained to me that I was watching the cultivated human heart cells organize themselves into a piece of tissue. The tissue beats in the dish. The metal pegs, once connected to a bioreactor, monitor the strength of the tissue in terms of how it stretches and beats. To make a bigger piece of tissue the lab members would have to start with more cells. Tissue is not grown, but rather assembled by the cells themselves.

Most of the basic science of developing and engineering different stem cell types is done at this laboratory. However, Frederic, the laboratory director explained that undertaking interspecies chimera research requires not just basic science but also the expertise of clinicians, surgeons, animal husbandry experts, biomedical engineers and chemists. While dish models of cells are a vital component of the project, Frederic remarked that "we cannot

5 John Gurdon and Shinya Yamanaka were awarded a Nobel Prize in Physiology or Medicine in 2012 for the discovery that mature cells can be reprogrammed to become pluripotent (Gurdon, 1962; Takahashi and Yamanaka, 2006).

make functional organs in a dish". The dishes marked with 'h' for human are limited to making different cell types and engineering tissues. This is where the idea of the chimera comes in – Frederic explained that non-human–animal bodies might be a solution to the challenge of generating the complex cellular structures of organs. As opposed to the dish with two titanium pegs holding the human heart tissue in place and placed in the bioreactor, an animal host would constitute the biologically active environment for tissue and organ development.

The move from modelling human material in a dish to cultivating tissues or a whole organ of one species in the body of another greatly expands the technical and practical considerations of the consortium's research project. The majority of work on mammalian interspecies chimeras has been done in mice and rats. Humans differ considerably from mice and rats in embryo size, speed of development and gestational period. Such differences mean that researchers need larger animal hosts that share more similarities with humans in terms of organ size, anatomy and reproduction. Pigs, sheep and monkeys are the animals that more closely align with humans.

In stem cell labs however, large animals such as pigs, are not part of the technical infrastructures. Given this, Frederic, Sophie and the other stem cell researchers collaborate with a nearby farm animal research institute for access to pigs and knowledge about their use as experimental animals. Pigs are ideal for their research, Frederic explained because physiologically they are similar to humans (in principle it is only non-human primates that are more similar). The pig also reproduces well and relatively fast which is important if you want organs. Stefan, the director of the farm animal research institute, described the role of the pig in the chimera project as "a type of living bioreactor". However, Stefan who is a world leading expert on pigs as experimental animals, explained there are many challenges with using pigs in this type of research. One significant problem was what he called "the reign of the mouse". As the history of experimental mammalian chimeras shows (remember Tarkowski's 'hero mice') the mouse is an extremely well-defined model organism in basic science. Whereas the genetics, reproductive and developmental pathways of the mouse are well established, in the pig they are not. For example, the mouse genome was sequenced in 2002 and the pig genome in 2012. While the first embryonic stem cell lines were derived from mice in the early 1980s, researchers are still struggling to produce pig embryonic stem cells that are pluripotent.

The making of interspecies mammalian chimeras then requires much more research on the functional biology of the pig despite the impetus of the research being based on improving human health. This dilemma faced by the researchers mirrors the history of cell culture and stem cell biology more broadly. In her account of how cells came to live separately from the bodies they originally came from, Hannah Landecker (2007, p. 223) shows how "developments with animal matter provided the material and conceptual infrastructure for later experiments with human matter". Her argument shows how if we only focus on human material we can easily miss the overarching technical and conceptual approaches of biology that make work on human biological material possible in the first place.

Not only does the work on human biological material often come at the end of the research, in many cases other species are used as proxies to predict how human material behaves outside the human body. While the desired goal of making interspecies mammalian

chimera is to insert human cells into a developing pig embryo, the research consortium was not actually using human cells. Instead, they were using cell lines from rhesus monkeys as a proxy for human cells. This was because the researchers were concerned about what, Felix, another member of the stem cell team aptly referred to as "unclear chimerisms". When the cells of one donor species are inserted into a developing host embryo it is extremely difficult to know where those cells are going to populate in the host animal. The concern for these researchers (and for all those engaged in this kind of research)[6] is that human cells could contribute not just to the targeted organ in the host animal, but provide potential gamete and neural contributions – resulting, for example, in a pig with human brain tissue. At this stage it is very difficult to control and predict how and where human cells will populate in another species. This is the problem of 'unclear chimerisms', or what a more recent publication on mammalian interspecies chimera called "off-target" humanized tissue (Wu *et al*, 2016, p. 56).

This problem of unclear chimerisms, or off-target humanization illuminates the paradoxical status of human biological material that I repeatedly encountered in fieldwork. Making other entities more human (or human-like) is at once desirable (a pig with a functional human organ to save a human life) but can simultaneously be an ethical abomination (a pig with a human brain). As research moves from dishes marked with 'h' for human into more intricate material entanglements with other species involving organs and bodies, the relationship between the plasticity of biology and the human person comes into question. To this extent, chimeric forms of life are harbingers of anxiety, especially when they contain human biological material.

Returning to Landecker (2007, p. 233) however, before we exclaim over the potential for new biological technologies to transform or impact what it means to be human, we first must "consider how biotechnology changes what it means to be biological", and by extension of that, what it means to be human. When it comes to the question of the human in biological life, Landecker (2007, p. 235) formulates the central question this way: "what is the social and cultural task of being biological entities – being simultaneously biological things and human persons – when 'the biological' is fundamentally plastic?". Landecker's question requires us to consider not just the fundamental plasticity of biology, but also this category

6 For example, in late September 2015, the National Institutes of Health (NIH) in the United States declared a moratorium on funding chimeric research where human stem cells are inserted into very early embryos from other animals. However, similar to other instances where federal research monies were removed from controversial research (e.g. human embryonic stem cell lines), such research can continue, but with private monies. The moratorium was met with scepticism and criticism of researchers working in this domain who, in a letter to *Science*, argued that such a moratorium impeded the progress of regenerative medicine (Sharma *et al*, 2015). In 2016, the NIH announced that it would replace the moratorium with a new kind of review for specific types of chimera research, including experiments where human stem cells are mixed with non-human vertebrate embryos and for studies that introduce human cells into the brains of mammals (except rodents, which will be exempt from extra review). These experiments will go to an internal National Institutes of Health steering committee of scientists, ethicists, and animal welfare experts that will consider factors such as the type of human cells, how they will populate in non-human organisms, and whether they may change an animal's behaviour or appearance.

of the human person. The experiences of those working in the research consortium can attest to the fundamental plasticity of biology. This plasticity however, also raises the spectre of unclear chimerisms and brings into question what constitutes a human person.

Human persons and unclear chimerisms

The research practices described above reflect how translational biomedical research further opens up potentials for chimeric life as areas such as genomics, animal models, structural biology, biochemistry and molecular biology advance new understandings about the diseases and illnesses that break down our bodies. The problem of unclear chimerisms identified by members of the research consortium are connected to a wider set of deliberations taking place across stem cell science about the meaning and significance of human biological material and its connection to the human person. For example, over the last 10 years, almost all countries that invest in life sciences research have issued detailed reports on the problems that chimera-based research brings to law, ethics and regulation (e.g. Academy of Medical Sciences, 2011; Danish Council of Ethics, 2007; Singapore Bioethics Committee, 2008). The arresting similarity between these texts is the manner in which the human research subject is contrasted to the animal. Humans are biological animals, but they are not considered so in the juridical structures governing biological research (see Hinterberger, 2016).

While the ontological premises of biology may be undergoing major revision (Müller-Wille and Rheinberger, 2012; Meloni, 2016), so too are the institutional structures within which researcher's practice. These changes involve not only reformulations of public/private relationships, regulatory structures and institutional organization, but also changing approaches to what and who counts as a human research subject (Haraway, 1997; Rabinow, 2002; Sunder Rajan, 2006; Rose, 2007; Pálsson, 2007; Cooper, 2011). This is the world of translational research (Sunder Rajan and Leonelli, 2013). In the United States, Embryonic Stem Cell Research Oversight Committees form part of these new regulatory structures. These committees are similar to institutional review boards found at most major American research universities. However, unlike institutional review boards, where there is a relatively clear subject outlined for protection, (the human subject) those sitting on oversight committees have been asked to deliberate on the extent to which experiments may give "human contributions" to other animals (National Academy of Sciences, 2010, p. 32). That is, if a scientist's work uses human materials, such as embryos, or stem cells derived from human embryos, this committee must investigate the extent to which the humanisation of other life forms may occur within proposed experiments.

There are no established metrics of humanization at molecular and cellular levels. While visiting a major American research university, with its own oversight committee, I met a lawyer who told me about an informal conversation he had with a colleague. This colleague, a senior bioethicist, was expressing frustration at the hyperbolic modes of debate accompanying human embryonic stem cell research and the making of chimeras. He said: "stem cells are a smudge. That's it". This lawyer, though feeling similarly tired by the debates, but less reductive, replied with this creative prompt "Well, if they are just a smudge, would you eat them?" His colleague did not want to take up this challenge of cellular gastronomy. The lawyer replied "so then stem cells are something…" The lawyer told me this story because he wanted to make a point - that human cells were not merely a smudge,

but nor did they fit into the neat divisions that accompanied his professional world which was divided into human research subjects, animals and human embryos.

The humanized forms of life now under deliberation in most advanced liberal democracies separate from the human body, human properties, such as cognition, and assess how and whether they might turn up in chimeric life. Take, for example, mice with human brain cells. Researchers at the University of Rochester (Han *et al*, 2013) created mice with human glial cells in their brains (glial cells support neurons, the 'thinking' cells of the brain). These humanized mice are described in publications as smarter than their regular brained mice counterparts. At the same time, however, the researchers argue that there is nothing particularly human about these mice with human glial cells in their brains:

> This does not provide the animals with additional capabilities that could in any way be ascribed or perceived as specifically human. Rather, the human cells are simply improving the efficiency of the mouse's own neural networks. It's still a mouse (Goldman quoted in Loike, 2015).

The question, however, of whether or not interspecies chimera may retain behavioural traits characteristic of the donor species - in this case human cognative capacities in a mouse - remains unclear and under deliberation amongst researchers (Wu *et al*, 2016, p. 51). Mark Dowie (2004) has previously written that, at times, these deliberations mirror the famous phrase issued by United States Supreme Court Justice Potter Stewart to describe his threshold test for obscenity in pornography: "I'll know it when I see it".

While the category of the human research subject has a distinct and fairly recent genealogy in contemporary Euro-America (Stark, 2011), it appears that changes are afoot in understandings of what this subject materially constitutes. Key faculty involved in ethical and regulatory oversight at one of America's top research universities are debating the status of human stem cells by considering whether they would ingest them. So called 'smart mice' with humanized brains are smarter than regular mice, but have nothing specifically human about them. All this suggests there may be some strange times ahead. What is emerging as curious and, often unknown, are not the liminal creations of biology typified by chimeric life, but idea of human itself. Chimeras, it turns out, are less curious than they first appear, forming a rather regular figure in biology. Instead, it is the category of human that is becoming increasingly elusive, fragile and unknown as it becomes entangled in chimeric life.

The politics of the human in bioscience

We can begin to draw out the significance of chimera-making technologies in bioscience by examining literature which explicitly argues for a renewed engagement with the human. This literature, which includes, but also extends beyond the social studies of bioscience, cuts across the humanities and social sciences, emphasizing our shared vulnerability and precariousness with other living beings (Phillips, 2015; Braidotti and Gilroy, 2016; Cornell and Seely, 2016). In explicitly focusing on how some human lives come to be valued more than others it places the question of the human at the heart of politics – rubbing up against what Paul Gilroy (2014, p. 23) calls "today's assertively post-human mood". For Gilroy (2011, p. 10), the widespread hasty dismissal of humanism trending in academia needs to be

met with "an obligation to re-engage/re-enchant the human" – one that places an analysis of racial hierarchy at its centre. In feminist science studies, Deboleena Roy and Banu Subramaniam (2016, p. 34) have remarked that while they do not argue for the centrality of the human, the post-humanist slant under which some feminist uses of biology are now proceeding, may not fully situate biologies "*in* their political and historical context". While differing in emphasis and analytical plans for action, these literatures offer space to reflect on the transforming politics of the human in bioscience.

One significant insight they offer is that biological metaphors or activities cannot provide the basis for renewed socialities or political commitments (e.g. Phillips discussion of humanism and posthumanism, 2015: 107–136). Along these lines, Drucilla Cornell and Stephen Seely (2016, p. 210) argue for less time being spent on "de-bunking 'the human'" and more attention to the 'undertaking of Man' through a new collective praxis of being human. They sketch out this collective praxis of being human through the work of philosopher, Syliva Wynter. Drawing on figures such as Aimé Césaire, Franz Fanon and Edward Said – who all held commitments to humanism, Wynter develops a critical genealogy of colonial institutions and the human in Western thought which leaves behind 'Man' but still sees a future that requires and ethically demands new expressions of humanness. Her work draws out the contradictory force that biological thought has in relation to the human. Darwin dispelled the premise that humans had any God-given attributes that separated them from other animals. Yet, this position of continuity with all organic life went hand in hand with the development of divisions between those who were "selected by evolution" and those "dyselected by evolution" so as to classify humans through hereditary variation and racial orders (Wynter in Scott 2000, p. 204). A politics of the human then means making more explicit 'our genres of being human' that are not necessarily connected to biological notions of 'Man' (Wynter in Scott, 2000).

Recent work in the social studies of the biosciences have illuminated collective practices of being human that differ substantially from the traditional assumptions about what underpins a human person (often seen as the capacity for moral reasoning). Across different research sites (a neonatal ward, a nursing home and pig laboratory), Svendsen *et al* (2017) chart numerous collective practices of doing the human that move beyond static ideas of human persons. Through their detailed ethnographic study, they show how "border, edge and maintenance practices in doing the human force open our all to generic western category of 'the human'" (2017). Similar to Svendsen *et al*.'s focus on enacting the human, this account of making interspecies mammalian chimeras shows how understandings of humanness or human attributes, particularly at the level of cells and tissues does not take us beyond the human, but rather into the heart of how this category continues to shape research and elicit new forms of deliberation. Such reengagements with the makings and doings of the human offer the social studies of bioscience tangible ways to explore what Jamie Lorimer (2016, p. 57) has recently called "more-than-human, but not posthuman" achievements.

Engaging with the technical and ethical work required to maintain boundaries around the human illuminates the historical and institutional specificities that underpin the human research subject in biomedical science. Charis Thompson (2013) has charted the "ethical choreography" required to maintain boundaries around the human research subject as it becomes entangled in stem cell science. The constitution of the human research subject, she explains, is rooted in modern bioethics and can be dated from the Nuremberg trials where

doctors were accused of war crimes and crimes against humanity: "Nazi Germany remains the moral nadir and the geopolitical locus of much of the bioethical imaginary" (2013, pp. 191–199). The kinds of juridical structures that undergirded this human subject however also brought into being a new kind of experimental subject, specifically the "non-human animal" as the mandatory "substitutive research subject" (Thompson, 2013, p. 191). With the making of interspecies chimera, this imaginary gives way to practical realities in the laboratory for the experimental animals who are scarified because of substitutive research logics. The fieldwork recounted in this article shows how these substitutive logics undergird research – when the dish can no longer provide the infrastructure for modelling complex organs an animal host body becomes a living bioreactor. Where the use of human cells may be prohibited, monkey cells are used as a proxy for what human cells will do.

Holding the figure of the chimera up to the light illuminates long-standing interconnections between scientific and mythical modes of thought. As one form of chimeric life, interspecies mammalian chimera usher in new conversations about what and who constitutes the human in biomedical research. The result is that substantive notions of humanness, rather than being dissolved, are being re-articulated in the biosciences. The redefinition of human functions and processes, particularly at the level of cells and tissues, sits uneasily with the assumption that substantive notions of the human, with all the documented ways such assertions have led to hierarchical ideas, are part of our historical past. Experimental chimeras are part of the post-genomic era which has ushered in a reformulation of life processes and offered new definitions of what constitutes an organism. Yet scientists are being asked by regulators and governments to identify and isolate possible human contributions to other animals and entities. In contemporary politics, it's perhaps not that the boundaries between human and non-human are blurring - rather the forms of life given value and recognition in these opposing peripheries are undergoing transformation.

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